ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

1954

243 CHARLES STREET

BOSTON, MASSACHUSETTS

STAFF

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Jin H. Kinoshita, Ph.D.: *Instructor in Biochemistry*

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THE HOWE LABORATORY is now twenty-two years old or older depending on one's point of view and definitions, for founding a laboratory is like writing a book or having a baby — the official inauguration is really the end of a series of responsible events. These have just been recapitulated by Dr. F. H. Verhoeff, the first Director of the Laboratory, in an address dedicating the Proctor Laboratory in San Francisco. Our present attempt to bring the methods and knowledge of the basic sciences to bear on clinical problems is basically similar to that of 1932 when the Howe Laboratory first occupied quarters at the Massachusetts Eye and Ear Infirmary. It is an exciting and satisfying approach which has brought a measure of benefit to many and has advanced the frontiers of knowledge to a respectable degree.

RESEARCH ACTIVITIES

The physiology and pathology of the flow of aqueous humor in and out of the eye have been further pursued by Dr. Grant. Previous studies in this Laboratory based on tonography have shown that the most significant control over the intraocular pressure is exerted by the resistance to outflow. Inadequate facilities for drainage of aqueous humor are responsible for the increase of intraocular pressure in glaucoma. In correlation with the investigations on patients, Dr. Grant has for several years been carrying out perfusion studies on enucleated eyes in a fundamental analysis of the factors which control the outflow of aqueous humor. Interestingly enough, the resistance to outflow is only slightly less after enucleation than prior to enucleation.

Owing to anatomic and physiologic differences between animal and human eyes, these studies have been carried out, so far as possible, on human eyes acquired through the Boston Eye Bank. Although unsuitable for use in corneal transplantation, these eyes have had normal outflow systems. It is hoped in the future that persons with glaucoma will choose to leave their eyes for study so that comparable measurements may be made on eyes with abnormal outflow systems.

By correlating the resistance to outflow with serial dissections of the angle region, the anatomic site of the resistance for normal eyes is being narrowed to a very small region. But the crucial study of the site of resistance to outflow in glaucomatous eyes must wait until such eyes become available for comparable experiments. Unfortunately those eyes which have to be removed because of pain are in such an advanced stage of glaucoma as to be unsuitable for such a study.

Clinical studies have been concerned primarily with improving the treatment of glaucoma. The rational use of peripheral iridectomy in angle-closure glaucoma and an understanding of many of the clinical features of this type of glaucoma followed a series of gonioscopic and tonographic studies by Drs. Grant and Chandler. Further therapeutic trials are being made on a number of new drugs by Dr. Trotter. Aside from diamox, which was mentioned in last year's REPORT, observations are being made on the antiglaucomatous effects of neohydrin, dibenzyline, thorazine, and reserpine. Preliminary clinical studies have also been carried out by Dr. Trotter in association with Dr. Leydecker (Bonn, Germany) on the modus operandi of a provocative test for glaucoma utilizing priscoline.

Approximately two years ago a comprehensive study of fat metabolism was begun by Drs. Cogan and Kuwabara. By the time of last year's REPORT the results were sufficiently promising to suggest a possible application to the general problem of arteriosclerosis in addition to the particular problems of the eye. Specifically it was found that all the cells of the cornea showed an extraordinary capacity to synthesize fat when exposed to oleic acid in the presence of serum. The resulting deposition of fat appeared similar to that which occurs in atheroma of blood vessels or in a variety of degenerative processes throughout the body, as well as in certain diseases of the cornea. Since oleic acid is a natural constituent of the body and is known to be present in excess in certain conditions associated with atheroma formation, it seems altogether possible that the discovery of this process in the eye has a wide biologic significance.

It is, however, one of those recurrent paradoxes in research that the ultimate result has no bearing on the subject which was responsible for its initiation. Thus the fat of arcus senilis which was the original focus of attention appears to arise by a process other than synthesis in situ. On the other hand, the present observations do appear to apply to the deposition of fat in other forms of lipidosis corneae and to the fat found in diverse necrotizing processes. Pilot experiments on non-ocular tissues, particularly brain and liver, have yielded results similar to those which occurred in the eye and have also provided potentially useful information on such related subjects as intracellular enzyme activity and lipophagocytosis.

The experiments were regrettably interrupted by Dr. Kuwabara's forced return to Japan for a few months, but he is now back in this country on what we hope is a permanent basis and has again picked up the threads of the investigation with his customary industry and ingenuity. There is reason to believe that this study will yield results of considerable consequence.

Since the day, not so long ago, when the lens was considered the seat of vision, the unique properties of this organ have intrigued investigators. Its cytologic isolation from the rest of the body, its transparency which is all the more extraordinary in view of its high protein content, and its accommodative power which varies so precisely with age and which we all take for granted until we lose it, are all properties that are scarcely matched by any other tissue. Even without the practical stimulus of cataract formation, these properties have indicated the importance of understanding the normal processes that make the lens what it is. Recent investigations from numerous laboratories have emphasized the active metabolic nature of the lens and its dependence on physiologic processes similar to those elsewhere in the body. During the past year, however, Dr. Kinoshita has made a series of observations that point to a phase of lens kinetics differing substantially from that of most tissues in the body. Whereas other tissues derive most of their energy from the breakdown of glucose through a complex series of reactions collectively known as the citric acid cycle or Krebs cycle, the lens avails itself chiefly of a more direct metabolic pathway called the direct oxidative reaction with the formation of 5-carbon sugars (ribose) and 7-carbon sugars (heptose). It is by this method that oxygen is consumed and carbon dioxide given off from the lens. Why the lens should avail itself of this process in contrast to the usual method of other tissues remains to be seen, but it is of major interest and possible significance that the cornea appears also to utilize this direct oxidative method to a considerable degree.

There can be little doubt that this discovery will have important bearing on some of the unique functions of the lens and cornea; it has already explained a number of apparent inconsistencies in our prior knowledge of the biochemistry of the lens.

Studies which have been designed primarily to elucidate mechanisms of corneal injury by chemicals have been carried out by Dr. Kern in association with Dr. Grant. These studies have provided new information on the interactions of various ions with the corneal stroma. Early in the course of this work a practical result was achieved in the development of a new medical treatment for dissolving from the cornea the calcific opacities which may result from superficial burns of the eye by lime, as well as those which result from hypercalcemia and chronic uveitis. Clinical usefulness of this treatment has now been confirmed by other investigators. Another result of these investigations has been the finding that ions interact with the cornea not only under toxic conditions, but also physiologically, and that the mucopolysaccharides of the cornea have an important part in this reaction. The significance of this interaction with regard to corneal turgescence and transparency has not been established, but is currently being studied.

Other toxicologic studies which have been underway in the Laboratory for some time relate to poisoning and blindness which is produced by methyl alcohol. In this connection Dr. Kinoshita has demonstrated the presence in the retina of human beings and animals of a specific enzyme system for oxidation of formaldehyde, which is thought to be a toxic intermediary in methyl alcohol poisoning. (This enzyme had previously been discovered in the liver by Dr. Strittmatter of the Department of Biochemistry of Harvard Medical School.) Dr. Grant has for some time been studying the systemic detoxication of formaldehyde in rabbits, and he has determined that administration of glutathione, which is a necessary coenzyme for Strittmatter's selective enzyme, augments the rate of detoxication. These observations raise a hope that glutathione may be beneficial in treatment of acute methyl alcohol poisoning in patients. Unfortunately methyl alcohol poisoning in animals is somewhat different from that in human beings, and it has been difficult to evaluate this potential treatment experimentally.

The perennial question of heredity versus environment in the manifestation of bodily abnormalities is being studied for the eye by Dr. Donaldson and a group of collaborators (Drs. Neil Thorlakson, Joseph Dowling, and Rameshwar L. Pahwa). Some sixty pairs of twins have now been examined and photographic records made of the anterior ocular segments and fundi. Eventually these records and others which it is hoped to obtain will be subjected to genetic study.

For the record it may be noted that Dr. Cogan was awarded in the past year the Proctor Medal by the Association for Research in Ophthalmology.

SERVICE ACTIVITIES

Believing that coordination of laboratories having overlapping functions was desirable, Dr. Cogan accepted the administrative responsibilities of the Eye Pathology Laboratory in addition to those of the Howe Laboratory for an indefinite period. The two laboratories will, of course, continue as independent units, but it is expected that there will be a mutually profitable exchange of services and functions between them. The operation of the Pathology Laboratory and much of the teaching is currently being carried on by Dr. Taylor Smith on a full-time basis. Once again Dr. Verhoeff has given invaluable assistance and consultation in the reorganization of the department which he organized over fifty years ago. A cross-reference system for cataloguing the cases is being introduced which should enhance the Pathology Laboratory's function as a place of research and study. Shortly it is hoped to be possible to accept Fellows for advanced training.

Drs. Trotter and Grant have continued to serve in informal consultative capacity to the services of the Massachusetts Eye and Ear Infirmary in the study and management of glaucomatous patients. There is some possibility of transferring these clinical activities from the Laboratory to the Infirmary as a regular Glaucoma Consultation Service with Resident training and Staff rotation, but as yet no action has been taken.

On the border between research and service functions is Dr. Donaldson's now well known developments in ophthalmic photography. The collection of stereophotographs taken with the Donaldson camera comprises an extraordinary reservoir of clinical illustrations that have been abundantly used for teaching and reference purposes. In addition, they have repeatedly won official commendation at various ophthalmic conferences as exhibits on special subjects. This year's Blue Ribbon Award made by the American Academy of Ophthalmology and Otolaryngology was granted for the unique exhibit of photographs of the angle of the anterior chamber taken through a gonioscopic lens.

In order to establish uniform and precise specifications for electronic Schiotz tonometers, Drs. Grant and Trotter have made numerous calibrations on human eyes both during life and following enucleation. This project undertaken in cooperation with the Committee on Standardization of Tonometers (of the Academy) became essential in view of the use of these tonometers in the now general practice of tonography.

Teaching which has for years been a correlative function and duty of all members of the staff has again occupied a significant role in both a formal and informal capacity. In addition, the Laboratory sponsored a lecture at the Harvard Medical School by Dr. Frank Walsh on "Lesions of the Third Nerve" while Dr. Walsh was Visiting Professor at the Harvard Medical School.

A novel gonioscopic lens has been developed by Drs. Grant and Chandler for direct observation of the angle of the anterior chamber during surgery. This is particularly serviceable in operations for congenital glaucoma of infancy.

The Howe Library whose operations are intimately connected with those of the Laboratory, has further grown in number of reader-visits (6,247 this year) and in circulation items (2,669) under the able and co-operative stewardship of Mr. Charles Snyder. Exhibits of various ophthalmic subjects are occasionally displayed in the Library, and Mr. Snyder prepared an interesting account of the first International Congress of Ophthalmology in connection with the meeting of this organization during the past year.

ORGANIZATION

In research, as in clinical practice, the satisfactions are many and the disappointments are many. Both erupt from unexpected sources and have a way of balancing one another with net gains, first in one direction and then in the other. Research on the eye is frustratingly slow for a field of such vital and practical import. The common appeal from desperate persons threatened with blindness underscores repeatedly and painfully the inadequacy of our accomplishments. Those small advances which we have made and which make up the substance of this and previous REPORTS are minute by comparison with the magnitude of the possibilities. With the prospective acquisition of new quarters permitting some expansion and more efficient operation it is hoped that some extension in the Laboratory's functions may be possible.

Needless to say it is a source of intense satisfaction to all of us that an impressive number of individuals, doctors and laymen, have taken upon themselves, without any solicitation, to contribute materially to the Laboratory. In these times of pressurized fund raising campaigns, this spontaneous gesture means much more than can be measured by material standards alone. To these individuals and to the various agencies which have supported specific projects, we are all inestimably indebted.

For general expenses:

The Massachusetts Eye and Ear Infirmary
Dr. and Mrs. Henry F. Allen
William P. Beetham, M.D.
Dr. Chester L. Blakely
Harry E. Braconier, M.D.
  (in memoriam: Dr. H. B. C. Riemer)
Virgil G. Casten, M.D.
Thomas Cavanaugh, M.D.
  (in memoriam: John and Sarah Cavanaugh)
Paul A. Chandler, M.D.
Julian F. Chisholm, Jr., M.D.
Thomas P. Cronin, M.D.
William F. Donoghue, M.D.
Edwin B. Dunphy, M.D.
Charles Dyson, M.D.
Thomas R. Gaines, M.D.
Mr. and Mrs. Frederick C. Hewlett
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Henry A. Mosher, M.D.
Abraham Pollen, M.D.

Mr. Clarence H. Porter
Marvin Posner, M.D.
Charles D. J. Regan, M.D.
Samuel A. Robins, M.D.
Benjamin Sachs, M.D.
David H. Scott, M.D.
Mr. and Mrs. Paul B. Tubby
Mr. J. M. Ulmer
Mr. Sam White

For studies on tonography and toxicology of the eye:
For studies of eyes in identical and fraternal twins:

U. S. Public Health Service

For studies on radiation cataracts:
For studies on metabolism of the ocular lens:

Atomic Energy Commission

For studies on intraocular fluids and glaucoma:

Mr. and Mrs. Albert I. Gordon
The Snyder Foundation

For studies on fat metabolism in the cornea and aging processes as reflected in the cornea:

The Massachusetts Heart Association
The American Heart Association

David G. Cogan, M.D.
Director

PUBLICATIONS

Cogan, D. G.

with Victor, M. Ocular signs of Wernicke's Disease. A.M.A. Arch. Ophth. 51: 204–211, February, 1954.

Ocular dysmetria; flutter-like oscillations of the eyes and opsoclonus. A.M.A. Arch. Ophth. 51: 318–335, March, 1954.

with Barrows, L. J. Platybasia and the Arnold-Chiari malformation. A.M.A. Arch. Ophth. 52: 13–29, July, 1954.

with Kuwabara, T. Lipogenesis by cells of the cornea. Science 120 (No. 3112): 321–322, August, 1954.

with Kuwabara, T. Metastatic carcinoma to eye from breast. Effect of endocrine therapy. A.M.A. Arch. Ophth. 52: 240–249, August, 1954.

with Norton, E. W. D. Spasmus nutans. A clinical study of twenty cases followed two years or more since onset. A.M.A. Arch. Ophth. 52: 442–446, September, 1954.

with Brockhurst, R. J. and Hynes, E. A. Crystalline dystrophy of the cornea. A.M.A. Arch. Ophth. 52: 458–459, September, 1954.

Donaldson, D. D.

A new camera for medical stereophotography with special reference to the eye. A.M.A. Arch. Ophth. 52: 564–570, October, 1954.

Grant, W. M.

with Trotter, R. R. Diamox (Acetazoleamide) in the treatment of glaucoma. A.M.A. Arch. Ophth. 51: 735–739, June, 1954.

with Chandler, P. A. An arrangement for gonioscopy during surgery. A.M.A. Arch. Ophth. 52: 454–455, September, 1954.

Kern, H. L.

Apparatus for chemical extraction of small pieces of cornea. A.M.A. Arch. Ophth. 52: 131, July, 1954.

Kinoshita, J. H.

with Masurat, T. The direct oxidative carbohydrate cycle of bovine corneal epithelium. Arch. Biochem. 53: 9–19, November, 1954.

Snyder, C.

First International Congress of Ophthalmology and Contemporary State of Ophthalmology in America. A.M.A. Arch. Ophth. 52: 264–271, August, 1954.

LECTURES

Cogan, D. G.

with Barrows, L. J. Platybasia and the Arnold-Chiari malformation. Presented by Dr. Cogan to the New England Ophthalmological Society, in Boston, Massachusetts, January 20, 1954.

Seminars to Fourth-Year Harvard Medical School students, in Boston, Massachusetts:

Ophthalmic disease. February 25, 1954.
Eye in systemic disease. March 4, 1954.
Neuro-ophthalmology. March 11, 1954.

Cogan, D. G. (*continued*)

Ocular manifestations of systemic disease. House Officers' Seminar, Massachusetts General Hospital, in Boston, Massachusetts, March 19, 1954.

with Fink, R. and Donaldson, D. D. X-ray induced cataracts on the lacrimal gland. Presented by Dr. Cogan to the Fifth Conference of the Committee on Radiation Cataracts, National Research Council, in Washington, D. C., March 26, 1954.

Ocular fundus. Postgraduate Course in Cardiology, Massachusetts General Hospital, in Boston, Massachusetts, March 30, 1954.

Lipogenesis in the Cornea. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 21, 1954.

Diabetic retinopathy. Postgraduate Course in Internal Medicine, Massachusetts General Hospital, in Boston, Massachusetts, June 17, 1954.

Pathogenesis of radiation cataract. Presented as part of Session on the Effects of Radiant Energy, International Congress of Clinical Pathology, Washington, D. C., September 9, 1954.

with Kinsey, V. E. Criticisms of the deturgescence theory of corneal transparency. Presented by Dr. Cogan as part of Symposium by Association for Research in Ophthalmology on Transparent Media of the Eye, XVII International Congress in Ophthalmology, New York City, September 13, 1954.

with Kuwabara, T. Fat formation in the cornea. Presented by Dr. Cogan at the XVII International Congress in Ophthalmology, New York City, September 13, 1954.

Conjunctival implants in the rabbit anterior chamber. Paper read at Dedication of the Laboratories of the Francis I. Proctor Foundation for Research in Ophthalmology, University of California, School of Medicine, in San Francisco, California, October 1, 1954.

Systemic ophthalmology. Lecture to House Officers, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, December 7, 1954.

Donaldson, D. D.

House Officer Lectures, Massachusetts Eye and Ear Infirmary.
  Tumors of the lids, conjunctiva, and cornea. March 18, 1954.
  Tumors of the iris. March 25, 1954.
  Diagnostic problems. March 30, 1954.

Medical stereophotography with special reference to the eye. Biological Photographers Association, Boston Chapter, in Boston, Massachusetts, May 25, 1954.

Grant, W. M.

with Trotter, R. R. Diamox in the treatment of glaucoma. Presented by Dr. Grant to the New England Ophthalmological Society, in Boston, Massachusetts, February 17, 1954.

GRANT, W. M. (*continued*)

Current studies on glaucoma. Buffalo Ophthalmological Club, in Buffalo, New York, March 11, 1954.

The prospects of the patient with glaucoma. Thirty-Second Annual Congress of the New England Council of Optometrists, in Boston, Massachusetts, March 16, 1954.

Classification and diagnostic procedures for glaucoma. Lecture to House Officers, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 8, 1954.

Lectures on Toxicology and Tonography in Lancaster Courses in Ophthalmology, in Waterville, Maine, August 27th and 30th, 1954.

with Trotter, R. R. Outflow of intraocular fluid (clinical aspects). Presented by Dr. Grant at the Council for International Organizations of Medical Sciences Symposium on Glaucoma, in Montreal, Canada, September 10, 1954.

with Trotter, R. R. Factors responsible for resistance to outflow of intraocular fluid. Presented by Dr. Grant at the XVII International Congress in Ophthalmology, New York City, September 16, 1954.

KINOSHITA, J. H.

The utilization of glucose by an alternate metabolic pathway in the corneal epithelium. Eastern Section Meeting of the Association for Research in Ophthalmology, in Philadelphia, Pennsylvania, February 18, 1954.

Glucose-6-phosphate utilization by the direct oxidative cycle in the corneal epithelium. Department of Biological Chemistry Seminar, Harvard Medical School, in Boston, Massachusetts, March 8, 1954.

Carbohydrate metabolism of ocular lens. American Chemical Society, in New York City, September 12, 1954.

TROTTER, R. R.

Eye conditions in pediatrics. Lecture to Children's Medical Service, Massachusetts General Hospital, in Boston, Massachusetts, January 13, 1954.

Gonioscopy. Lecture to House Officers, Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, February 18, 1954.

Comparison of the water-drinking test and tonography. Alumni Association Meeting of the Massachusetts Eye and Ear Infirmary, in Boston, Massachusetts, April 21, 1954.

with Chandler, P. A. Angle-closure glaucoma, subacute types. Presented by Dr. Trotter to the American Ophthalmological Society Meeting, in Glacier Park, Montana, June 18, 1954.

Eye conditions in pediatrics. Lecture to Harvard Medical School Postgraduate Course in General Pediatrics, Massachusetts General Hospital, in Boston, Massachusetts, June 21, 1954.

FORM OF BEQUEST

The Howe Laboratory of Ophthalmology is an independent department of the Harvard Medical School and is jointly supported by a restricted endowment of Harvard University and by the Massachusetts Eye and Ear Infirmary.

For the information of those who may wish to contribute to this Laboratory, a form of bequest is here set forth:

I GIVE AND BEQUEATH TO THE HOWE LABORATORY OF

OPHTHALMOLOGY..

DOLLARS TO BE APPLIED TO THE USES OF SAID LABORATORY.

Such bequests are managed by the Treasurer's Office of Harvard University, and the income is accredited to the Laboratory.